REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A. CLAIM AMENDMENTS

Claims 1-56 are requested to be cancelled, and Claims 57-69 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 57-69 are now pending in this application. No new matter is added to the application through the addition of these new claims, which are supported in the Specification as follows:

Claim	**Limitations Not Previously Presented**	**Examples of Specification Support**
57	"introducing the composition directly into cardiac circulation"	Page 23, lines 26-27.
57	"the PLB protein is functionally attached to a transport peptide effective in facilitating translocation of a sufficient quantity of the protein into the myocytes"	Page 23, line 28-page 24, line 3.
58	"mutations of PLB constitute single or double point sense mutations to domains I or II of the PLB protein"	Page 17, lines 12-16; page 23, lines 11-13.
59, 60	PLB attached to *antennapedia* transport peptide; transport peptide is SEQ.ID.No. 7.	Page 24, lines 13-15; page 28, lines 22-23.
61	Molecule "...further comprising a cargo peptide and a linker attaching the cargo peptide to the transport peptide."	Page 28, lines 19-20; page 29, lines 5-11.

Claim	Limitations Not Previously Presented	Examples of Specification Support
62	"...the cargo peptide consists of the first 16 residues of an amino acid sequence selected from the group consisting of SEQ.ID.Nos. 8, 17, 18 or 19."	Page 25, lines 25-28.
63	PLB mutation "...consists of one selected from the group consisting of V49A, SE16, SN16, K3E and K3E/R14E, made to the amino acid sequence of SEQ. ID. No. 1 [wild-type PLB]." Each mutation is reflected in, respectively, SEQ.ID.Nos. 2-6.	Page 17, lines 12-16.
69	Direct introduction into cardiac circulation is by cardiac catheterization.	Page 23, lines 26-27.

No new subject matter being introduced by this amendment, its entry is respectfully requested.

B. RESPONSE TO LACK OF UNITY OBJECTION

Applicants respectfully submit that the lack of unity objection is now moot in view of the presentation of a new claims set drawn to the inventive method for using peptides in therapy, and the filing of a divisional drawn to the inventive method for gene therapy.

C. RESPONSE TO REJECTION OF CLAIMS 1, 4, 12, 16, 19, 20, 22, 23, 40-56 UNDER SECTION 112, FIRST PARAGRAPH (Enablement)

Applicants respectfully submit that the enablement rejection is now moot in view of the presentation of the foregoing new claims set. However, for the purposes of expediting prosecution, Applicants offer the following observations with respect to why the questions raised in the previous Office Action with respect to enablement are not germane to the current claims.

The Office Action takes issue with two particular aspects of the invention as claimed: (1) whether the *in vitro* data presented indicates that the invention will work as claimed; and (2) whether the constructs delivered according to the invention will be taken up by target cells (cardiomyocytes) in sufficient quantities to produce a desired effect. Applicants respectfully submit that one of ordinary skill in the art would reasonably expect the invention, as it is now claimed, to work as described. As such, the claims are enabled by the teachings of the Specification, in view of the skill in the art.

With respect to the data presented, the Office Action avers that "the specification admits that the results with the only peptide tested in vitro were not statistically significant." (Action, at page 4, emphasis added). Applicants submit that this is an incorrect restatement of the disclosure, which provides test results from *in vitro* experiments using not just one, but **two** different PLB/ transport peptide constructs: a PLB / *antennapedia* transport peptide construct (Example 4), and a PLB / penetratin construct (Example 5).

Although results varied, cardiomyocytes treated with the PLB/ penetratin construct "demonstrated a trend toward a larger, faster contraction in the myocyte" (page 31, lines 9-11). Given the trend demonstrated in the penetratin experiments, it cannot be said that the peptide construct did not work—indeed, it did translocate and, in more cells than not, did assert a functional enhancement on contractility in the cell. However, the Examiner finds these results to be unpersuasive in demonstrating that the invention will work as claimed.

Yet in making the enablement rejection, the Office Action fails to address the results obtained using the *antennapedia* construct. These data demonstrate that "[t]he PLB inhibitor molecule was translocated efficiently into isolated neonatal rat cardiomyocytes, and showed a resulting enhanced contractility of the cell." (Page 30, lines 11-14; see also, Figures 5A and 5B). Therefore, the Specification does provide a teaching sufficient to allow one of ordinary skill in the art to conclude that the claimed method can be used as described.

Moreover, the ability of such peptides to facilitate transport of molecules across the cell membrane was known at the time that the present application was filed (see, e.g., Derossi, *et al., J. Biol. Chem.*, 271(30): 18188-18193, 1996 [see, Supplemental IDS submitted herewith]). With respect to the heart in particular, Applicants' assertions in this respect are consistent with experience in the art with transport peptides (such as the *anntennapedia* peptide, the R7 peptide, and Tat) used to facilitate delivery of molecules into the heart (see, e.g., Chen, *et al., Chem.Biol.,* 8(12):1123-1129, 2001 [see, Supplemental IDS]). Therefore, based both on the teachings of the Specification (including the experimental results reported in Example 4) and existing knowledge in the art, those of ordinary skill would reasonable expect the invention to work as described and presently claimed by Applicants. The claims are therefore enabled.

The Office Action also questions whether the protein can be delivered to cardiomyocytes—the targeted cells—versus "all living cells in the body." (Action, at page 7). Without agreeing that those of ordinary skill in the art could not practice the invention as claimed with sufficient targeting of cardiomyocytes, Applicants submit that the Examiner's concern is fully addressed by the limitation of the claims to introduction of the inventive composition to the heart via cardiac-limited circulation. As taught in the Specification and known in the art, localized drug delivery to the heart using well-known means (e.g., infusion, injection, drug eluting stents, coated balloon catheters) can achieve high and sustained local concentrations of drug without use of large systemic doses (see, e.g., Specification at page 23, lines 26-27; Bailey, S.R., *Prog.Cardiovasc.Dis.,* 40(2):183-204, 1997 [paper reviewing the state of the local cardiac drug delivery art prior to the filing of the present application; see, supplemental IDS]; and, Chen, *et al., Chem.Biol.,* 8(12):1123-1129, 2001 [perfusion delivery of peptides into cardiomyocytes of intact hearts using a transport peptide; see, Supplemental IDS]).

For all of the foregoing reasons, Applicants respectfully submit that the present claims are fully enabled by the Specification, and so request that they be allowed.

D. RESPONSE TO REJECTION OF CLAIMS 1, 4, 12, 16, 19, 20, 22, 23, 40-42, 45-48 AND 52-56 UNDER SECTION 112, FIRST PARAGRAPH (Written Description).

These formerly pending claims were rejected as lacking written description support for the use of receptor-dependent transport peptides. The rejection is now moot in view of the absence of the receptor-dependent language in the present claims set.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date April 28, 2006

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